LEXSEE 1993 U.S. DIST. LEXIS 13928

GLAXO, INC. and GLAXO GROUP LIMITED, Plaintiffs, v. NOVOPHARM LTD., Defendant.

No. 91-759-CIV-5-BO

UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF NORTH CAROLINA, RALEIGH DIVISION

830 F. Supp. 871; 1993 U.S. Dist. LEXIS 13928; 29 U.S.P.Q.2D (BNA) 1126

September 17, 1993, Decided
September 17, 1993, Filed

CASE SUMMARY:

PROCEDURAL POSTURE: Plaintiffs sought an injunction to bar further infringement by defendant of plaintiffs' patent that covered a particular crystalline form of a chemical compound called ranitidine hydrochloride was tried before the court. Defendant admitted infringement but raised defense of patent's invalidity.

OVERVIEW: Plaintiffs owned a patent that covered particular crystalline form of ranitidine hydrochloride. Defendant infringed plaintiffs' patent by filing Abbreviated New Drug Application with Food and Drug Administration. In this application, defendant sought to market ranitidine hydrochloride seven years before patent's expiration date. Defendant attempted to prove patent was invalid due to inherent anticipation, inequitable conduct, and failure to disclose best mode. The court found that defendant failed to prove inherency because an example from prior patent that described process for making ranitidine hydrochloride crystals did not produce invariable results. The court determined that defendant failed to prove inequitable conduct because evidence regarding one declaration demonstrated no intent to deceive the patent examiner. Other declaration contained no misrepresentations of fact. Finally, the court concluded that patent was not invalidated based on a best mode violation because only the knowledge of the inventor listed on the patent was relevant, and she was unaware of best manufacturing procedure for pharmaceutical use.

OUTCOME: The court held that defendant infringed plaintiffs' patent, and plaintiffs' patent was not invalid. The court ordered approval not be granted to defendant to sell crystalline form of ranitidine hydrochloride until plaintiffs' patent expired. The court rejected defendant's arguments that plaintiffs' patent was invalidated by anticipation, inequitable conduct, or failure to disclose best mode.

CORE TERMS: patent, ranitidine, hydrochloride, experiment, declaration, chemist, pharmaceutical, crystal, examiner, azeotroping, x-ray, composition, covering, hydrochloric acid, diffraction, inequitable conduct, inventor, powder, seed, invention, disclose, infrared, salt, crystalline, anticipated, spectrum, hydrogen chloride, notebook, methyl, heat

LexisNexis(R) Headnotes

Evidence > Procedural Considerations > Burdens of Proof > Clear & Convincing Proof
Patent Law > Infringement Actions > Burdens of Proof
Patent Law > Infringement Actions > Defenses > Patent Invalidity > Validity Presumption
[HN1] There is a statutory presumption that an issued patent is valid, *35 U.S.C.S. § 282,* and a party challenging the patent bears the burden of proving invalidity by clear and convincing evidence.

Patent Law > Anticipation & Novelty > Accidental Anticipation & Inherency
Patent Law > Anticipation & Novelty > Elements
[HN2] Under *35 U.S.C.S. § 102,* an invention may be patented only if it is novel. Novelty is judged by examining the prior art available to the public at the time the patent application is filed. The prior art includes the teaching from an existing patent. If a unit of prior art discloses an invention, then the invention is said to be anticipated by the prior art. The prior art need not expressly disclose the invention. If an inventor seeks to

claim an advantage or modification that flows necessarily from a prior art reference, the reference inherently anticipates the inventor's claim, even if the advantage was not appreciated by the inventor of the prior art. In order for a claim to be inherent in the prior art it is not sufficient that a person following the disclosure sometimes obtain the result set forth in the claim, it must invariably happen.

Evidence > Procedural Considerations > Burdens of Proof > Clear & Convincing Proof
Patent Law > Anticipation & Novelty > General Overview
Patent Law > Inequitable Conduct > General Overview
[HN3] Inherency is not established by possibilities or probabilities. The mere fact that certain things may result from a given set of circumstances is not sufficient.

Patent Law > Inequitable Conduct > Burdens of Proof
Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > Effect of Inequitable Conduct
[HN4] In order to render a patent unenforceable on the grounds of inequitable conduct, a party must show by clear and convincing evidence that the patentholder made a material misrepresentation to the patent office during the patent prosecution process, and that the misrepresentation was intentional.

Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > Elements
[HN5] Misstatements only constitute inequitable conduct if they are material and are submitted with intent to deceive a patent examiner.

Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > General Overview
[HN6] There is no room to argue that the submission of false affidavits is not material.

Patent Law > Claims & Specifications > Best Mode > General Overview
[HN7] The patent statutes require, in addition to disclosing the invention itself, the applicant disclose in the patent specifications the best mode for making and using the claimed invention. *35 U.S.C.S. § 112.* The purpose of this requirement is to assure that in exchange for the monopoly protection extended by the grant of the patent, the applicant has given the public full access to the invention once the monopoly's protection is gone.

Patent Law > Claims & Specifications > Best Mode > General Overview
[HN8] The best mode requirement imposes a duty to disclose not only the best mode of making the invention, but the best method of using it.

Patent Law > Claims & Specifications > Best Mode > Fact & Law Issues
[HN9] The statute refers only to the knowledge of the inventor, *35 U.S.C.S. § 112,* and the use of imputed knowledge is not permitted to meet the requirement.

COUNSEL: **[**1]** For Plaintiffs: Stephen B. Judlowe, William G. Todd, Janet B. Linn, HOPGOOD, CALIMAFDE, KALIL, BLASTEIN & JUDLOWE, New York, NY. Steven P. Lockman, Stuart J. Land, ARNOLD & PORTER, Washington, D. C. Joseph W. Eason, MOORE & VAN ALLEN, Raleigh, NC.

For Defendant: John E. Rosenquist, Robert F. Green, Jeffrey S. Ward, LEYDIG, VOIT & MAYER, Chicago, IL. John R. Wallace, KIRBY, WALLACE, CREECH, SARDA & ZAYTOUN, Raleigh, NC.

JUDGES: BOYLE

OPINIONBY: TERRENCE W. BOYLE

OPINION:

[*872] ORDER

Plaintiff Glaxo Group Ltd. is the owner of United States Patent No. *4,521,431* covering **[*873]** a particular crystalline form of a chemical compound called ranitidine hydrochloride. n1 The *'431* patent expires in 2002. Plaintiff Glaxo Inc. is the United States subsidiary of Glaxo Group Ltd. and is the exclusive U.S. licensee of the *'431* patent. Defendant Novopharm infringed this patent on August 9, 1991, by filing an Abbreviated New Drug Application (ANDA) with the Food and Drug Administration in which it sought to market ranitidine hydrochloride beginning in 1995. Plaintiffs (hereinafter referred to collectively as Glaxo) then filed this action requesting an injunction barring further infringement by Novopharm. Novopharm filed an answer in which **[**2]** it admitted infringement, but raised as a defense that the patent was invalid.

n1 Glaxo markets ranitidine hydrochloride as antiulcer medication under the brand name Zantac.

The case was tried to the court starting on August 9, 1993. At trial, Novopharm contended that the *'431* patent is invalid for three reasons: (1) because the crystalline form claimed in the *'431* patent was inherently anticipated by an earlier patent held by Glaxo, (2) because Glaxo engaged in inequitable conduct in the prosecution of the *'431* patent, and (3) because Glaxo officials prosecuting the *'431* patent failed to disclose the best mode of processing ranitidine chloride for pharmaceutical use. Evidence was presented on each of these issues, and based upon that evidence the court decides the issues.

I. FACTUAL BACKGROUND

A. The '658 Patent.

In 1976 Glaxo chemists in Great Britain discovered ranitidine, an aminoalkyl furan derivative with histamine blocking capabilities, and began preparations for manufacturing and selling ranitidine **[**3]** as an antiulcer drug. An application for a patent covering the compound was filed with the patent office in the United Kingdom in 1976.

During the patent application process, Glaxo chemists attempted to synthesize a ranitidine salt. Salts are generally the preferred form of a compound for use in pharmaceutical manufacturing. On June 27, 1977, David Collin, a chemist at Glaxo's laboratories in Ware, U.K., discovered a process for making ranitidine hydrochloride, a salt of ranitidine, and recorded the method he had discovered in his notebook.

On July 25, 1977, Glaxo filed an application for a U.S. Patent covering all ranitidine compounds of a specified general formula, including ranitidine hydrochloride. That application resulted in the issue of United States Patent No. *4,128,658* (the *'658* patent).

Claim 18 of the *'658* patent covers ranitidine hydrochloride. The method for making ranitidine hydrochloride is set out at Example 32 of that patent. Example 32 was written based on Mr. Collin's work of June 27, 1977.

B. The *'431* Patent.

From 1977 to 1980, Glaxo's Chemical Development Department tested procedures for the commercial production of ranitidine hydrochloride. The procedure **[**4]** set out in Example 32 was not used in any of this work. A somewhat similar process, known within Glaxo as Process 3A, was used during the early part of the scale-up work, and in 1979, a more efficient procedure known as Process 3B was substituted for Process 3A.

On April 15, 1980, for unknown reasons, the thirteenth batch of ranitidine hydrochloride prepared using Process 3B produced crystals that were different from those previously produced by Glaxo. The differences between the prior batches and Batch 3B13 were confirmed by two analytic processes, known as infra-red spectroscopy and x-ray powder diffraction. Based on these analyses Glaxo chemists concluded that there were two crystal forms of ranitidine hydrochloride. Glaxo chemists designated the form produced on April 15 as Form 2 and the form produced in all prior batches as Form 1.

Glaxo eventually decided to proceed with the commercial development of Form 2 rather than Form 1, and modified Process 3B so that it regularly produced Form 2. The modified Process 3B was designated Process 3C by Glaxo chemists, and has been used by Glaxo to manufacture all the ranitidine hydrochloride it has sold Commercially.

[*874] On October 1, 1980, **[**5]** Glaxo filed a U.K. patent application covering Form 2. This application was Prosecuted for Glaxo by Elkington and Fife, a firm of patent agents in the United Kingdom. In 1981, Glaxo filed a U.S patent application covering Form 2, naming as the inventor Dr. Derek Crookes, the chemist who was in charge of the Chemical Development Department in 1980 when the first Form 2 was produced.

The patent examiner initially rejected the claims of Glaxo's Form 2 application and again rejected them on reconsideration. Grounds for the rejection were stated as "anticipated by or, in the alternative, . . . obvious over the *'658* patent, referring Specifically to Example 32.

In response to this rejection, Glaxo submitted two declarations which purported to show distinctions between the claims in the application and the prior art. After receiving these declarations, the examiner withdrew his rejections, and U.S. Patent No. *4,521,431* was issued, covering Form 2 ranitidine hydrochloride as characterized by its infra-red spectrum (Claim 1) and its x-ray powder diffraction pattern (Claim 2). In addition, the patent covers certain Pharmaceutical compositions (Claims 3-16) and treatment methods (Claims 17 and **[**6]** 18) using Form 2.

II. NOVOPHARM'S DEFENSES

As noted above, Novopharm admits that by filing its ANDA in 1991 it infringed on the '438 patent, but raises in defense its contentions that the patent is invalid. [HN1] There is a statutory presumption that an issued patent is valid, *35 U.S.C. § 282,* and the party challenging the patent bears the burden of proving invalidity by clear and convincing evidence. *Ethicon, Inc. v. Quigg, 849 F.2d 1422 (Fed. Cir. 1988).* Keeping these standards in mind, the court now turns to a discussion of Novopharm's challenge to the validity of the *'431* patent.

A. Inherent Anticipation.

[HN2] Under *35 U.S.C. § 102,* an invention may be patented only if it is "novel". Novelty is judged by examining the "prior art" available to the public at the time the patent application is filed. The prior art includes the teaching from an existing patent such as the '638 patent in this instance. *Graham v. John Deere Co., 383 U.S. 1, 6, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966).* If a unit of prior art discloses an invention, then the invention is said to be "anticipated" by the prior **[**7]** art. *RCA Corp. v. Applied Digital Data Systems, Inc., 730 F.2d 1440, 1444 (Fed. Cir. 1984).* The prior art need not expressly disclose the invention.

If an inventor seeks to claim an advantage or modification that flows necessarily from a prior art reference, the reference inherently anticipates the inventor's claim, *Stoller v. Ford Motor Co., 1991 U.S. App. LEXIS 1084, 18 U.S.P.Q.2D (BNA) 1545, 1547 (Fed. Cir. 1991),* even if the advantage was not appreciated by the inventor of the prior art. *In re Sovish, 769 F.2d 738 (Fed. Cir. 1985).*

In order for a claim to be inherent in the prior art it is not sufficient that a person following the disclosure sometimes obtain the result set forth in the claim, it must invariably happen. *Standard Oil v. Montedison, 664 F.2d 356, 372 (3rd Cir. 1981).*

Novopharm contends that Form 2 ranitidine hydrochloride, claimed in the *'431* patent, is inherent in Example 32 of the *'658* patent. As noted, Example 32 describes a process for making ranitidine hydrochloride, and was written based on David Collin's experiment of June 27, 1977, recorded in his notebook at page **[**8]** 122. n2

n2 The example reads:

EXAMPLE 32

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl] methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethynediamine hydrochloride

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl] methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethynediamine hydrochloride was dissolved in industrial methylated spirit 74 o.p. (200 ml) containing 0.16 of an equivalent of hydrogen chloride. Ethyl acetate (200 ml) was added slowly to the solution. The hydrochloride crystallized and was filtered off, washed with a mixture of industrial methylated spirit 74 o.p. (50 ml) and ethyl acetate (50 ml) and was dried at 50. The product (50 g) was obtained as an off-white solid m.p. 133 - 134.

[*875] In layperson's terms, the example tells a chemist to dissolve ranitidine base in industrial methylated spirit (IMS) (a solvent made up largely of ethanol) containing hydrogen chloride gas, then to add ethyl acetate, which is a cosolvent to aid in crystallization. As a result, crystals of ranitidine hydrochloride will form and precipitate **[**9]** from the solution. The crystals are then filtered out and dried.

It is Novopharm's theory that when the Example 32 procedure is faithfully followed, the product is, and always was, Form 2 ranitidine hydrochloride. Novopharm does not dispute that Mr. Collin performed the work shown in his notebook on page 122, or that his work produced Form 1.

Instead, Novopharm claims that Example 32 as written omits two critical and material steps that Mr. Collin included in his experiment on page 122. Consequently, Novopharm claims that when the prior art, Example 32, is practiced exactly as written, without the critical extra steps taken by Collin during his experiment of June 27, 1977, the product is always Form 2.

Simply put, Novopharm claims Glaxo never performed Example 32 precisely as written either before or after including it in the '638 patent. Novopharm theorizes if Glaxo had properly performed the example, the result would have been Form 2.

Novopharm claims that in reality it was the first party to faithfully practice Example 32. Novopharm contends the results of such practice under the prior art led Novopharm to the conclusion that Form 2 was anticipated by the *'658* patent and, consequently, **[**10]** this conclusion led Novopharm to the filing of its ANDA application in 1991.

In support of this contention, Novopharm called as witnesses tour chemists. n3 Novopharm contends the chemists repeatedly followed the Example 32 procedure and always achieved Form 2. These results were tested by infrared and x-ray spectroscopy. It is not disputed that the experiments Novopharm's witnesses ran did in fact produce Form 2. This, Novopharm argues, proves that Example 32, faithfully practiced, always results in Form 2. Based on this evidence, Novopharm seeks a finding

that the *'658* patent inherently anticipated Form 2 when Glaxo applied for the patent in 1977.

n3 The four chemists were Ildiko Riss, a research chemist at Novopharm, Dr. Xianglang Lu of Northwestern University, Dr. John Belletire of the University of Chicago, and Dr. Natalie Lazarowich of Dalton Chemical Laboratories in Toronto.

Glaxo attacked the validity of the results obtained by Novopharm's witnesses. Glaxo charges that Novopharm's experiments were contaminated **[**11]** with "seed" crystals of Form 2, and therefore, were not faithful replications of Example 32. Glaxo claims Novopharm's experiments were exposed to seeding from existing form 2 crystals and are unreliable; one, because either the ranitidine base used by Novopharm's scientists was impure, or two, because of airborne or surface seed contamination in the environment within which the experiments were conducted.

In all but one of the Novopharm experiments, the ranitidine base used as a starting material was synthesized by taking Form 2 ranitidine hydrochloride and using sodium hydroxide to "free" the base from the salt. Glaxo claims it is Scientifically impossible through this reduction procedure to remove all traces of Form 2 from the base and that seed crystals would necessarily remain.

A number of Novopharm experiments were conducted in areas where Form 2 ranitidine hydrochloride had been used, handled or manufactured. Glaxo contended that because submicroscopic seed crystals in these areas contaminated the environment this would inevitably be present in the air and on surfaces. Thus, the seed crystals would come in contact with the reaction mixture and affect the outcome of Novopharm's **[**12]** experiments.

Novopharm's witnesses insisted they had taken precautions to avoid seeding, and Doctors Lu and Belletire conducted their experiments in environments where only trace amounts of ranitidine hydrochloride, if any, had been present.

Dr. Lazarowych testified that because ranitidine hydrochloride is highly soluble in water and the method used for extracting the base from Form 2 required dissolving the **[*876]** salt in water, no ranitidine hydrochloride seeds could have survived the conversion to ranitidine base. Further, she testified with regard to experiments conducted in a "glove bag." There, extraordinary precautions were taken to avoid any potential for the introduction of airborne seeds. The court found this testimony credible, and finds that Novopharm's experiments were not affected by seeds of Form 2. Accordingly, Novopharm's evidence established that each time their witnesses practiced Example 32, the product was Form 2 ranitidine hydrochloride.

In response to this showing, Glaxo called David Collin. Collin testified that the work recorded in his notebook at page 122 was the basis for Example 32, and that infrared spectroscopy established the product of the page 122 experiment **[**13]** as Form 1. Novopharm contends that two of the steps Collin took were not reflected in Example 32 as written. First, the Collin experiment shown on page 122 contained a warming step not reflected in Example 32. Second, the notebook reflects Collin's reaction mixture as slightly acidic.

While it is true that neither warming nor variations in pH are addressed in the express language of Example 32, Collin testified to the example as an accurate summary of his work. He further testified that the differences in temperature and pH not shown in the example were only very slight, and that he did not believe these differences would affect the polymorphic form produced from practicing Example 32. The court found this testimony to be both credible and supported by other evidence presented during the trial.

With respect to the use of gentle heat, all of the expert chemists who testified for both sides, with the exception of Dr. Lazarowych, told the court it is acceptable practice, when dissolving a solid, to warm the mixture to bring the solid into the solution. Although she felt heat would generally be acceptable, Dr. Lazarowych testified such a process would be undesirable in this particular **[**14]** experiment because of the structure of the ranitidine molecule. Despite this belief, she used heat during her glove bag experiments to speed the dissolution process. The court finds the warming process is acceptable to a chemist skilled in the art while practicing Example 32.

With respect to the differences in pH, the court holds credible Collin's testimony that the pH of the experimental solution was slightly acidic. The evidence was that a chemist skilled in the art would not consider a slight excess of acidity to be outside the teachings of Example 32. The science of chemistry recognizes such minute variation may occur in the amounts and proportions of the ingredients when mixing an acid and a base, and therefore, some minor variation in pH is tolerated under the method used in Example 32 to produce the salt. The court finds the example not to require the reaction mixture to have a completely neutral pH prior to crystallization. n4

n4 Dr. Lazarowych presented her theory to the court that minor differences in pH when cou-

> pled with heat would affect the crystalline form resulting from the experiment. Because of the structure of the ranitidine molecule, she believes that ranitidine degrades after the application of slight heat within certain pH ranges, resulting in a different crystalline form when the reaction is complete. After weighing this testimony against that of other witnesses, the court is not persuaded that Novopharm made a sufficient showing on this point to prove by clear and convincing evidence that slight variations in temperature and pH in Mr. Collin's experiment would result in an entirely different polymorph from the practice of otherwise identical experiments.

[15]**

The court finds from the evidence that Example 32 is an accurate description of Collin's work. On June 27, 1977, Collin performed an experiment following a process later recorded in the *'658* patent as Example 32. The product of this experiment was Form 1 ranitidine hydrochloride.

Glaxo called as witnesses three chemists from Oxford University, who testified that after the commencement of this lawsuit they had prepared ranitidine base using one of the methods set out in the '638 patent. They then used this base as the starting material in three replications of Example 32. In each of these experiments, the product obtained was Form 1. This work, Glaxo contended, shows that when Example 32 is performed, the product of such example is Form 1.

Novopharm challenged the validity of the Oxford work. In one of the Glaxo experiments, Dr. Crouch testified that he seeded **[*877]** the solution with Form 1 crystals to induce crystallization. In a second experiment, he sought to induce crystallization by scratching the wall of his reaction vessel with a glass rod covered with some ranitidine base. The third experiment followed Example 32 closely except that the reaction vessel was warmed.

While the court **[**16]** agrees the first two of Dr. Crouch's experiments were contaminated by the introduction of Form 1 seeds and ranitidine base, the same is not true of his third experiment. Dr. Crouch was credible in his testimony that he only applied gentle heat to the reaction vessel in his third experiment to aid in the dissolution of the ranitidine base. The court finds that gentle warming is within the proper practice of Example 32.

Based upon these findings, the court concludes that Collin's experiment and Dr. Crouch's third experiment would both be considered by a chemist skilled in the art to be within the teachings of Example 32. When this conclusion is coupled with the court's findings concerning Novopharm's experiments above, the evidence as a whole shows that the proper practice of Example 32 has resulted at times in the exclusive production of Form 1 and at other times in the exclusive production of Form 2. The only practice of Example 32 at the time the *'658* patent was issued was Collin's page 122 experiment, and that clearly produced Form 1. The evidence does not support a finding that Form 2 invariably results from the practice of Example 32. [HN3] "Inherency is not established by possibilities **[**17]** or probabilities. The mere fact that certain things may result from a given set of circumstances is not sufficient." Rosenberg, Patent Law Fundamentals § 7.04. Novopharm has failed to carry its burden of proving inherency by clear and convincing evidence.

B. Inequitable Conduct.

Novopharm's second ground for contending the *'431* patent is invalid is their contention that Glaxo was guilty of inequitable conduct. [HN4] In order to render a patent unenforceable on the grounds of inequitable conduct, a party must show by clear and convincing evidence that the patentholder made a material misrepresentation to the patent office during the patent prosecution process, and that the misrepresentation was intentional. *Schering Corp. v. Optical Radiation Corp., 867 F.2d 616 (Fed. Cir. 1989).*

Novopharm's charges of inequitable conduct stem from the submission of two declarations in response to the patent examiner's August 28, 1983 rejection of Glaxo's Form 2 patent application. In that rejection, the examiner said

> Claims 1 and 2 are rejected under *35 U.S.C. 102*(e) as anticipated by, or as being obvious over, Price et al **[**18]** *4,128,658*. Price et al discloses (example 32) and claims (claim 18) [ranitidine]. The present claims are drawn to a specific form of this compound. Applicants' argument have [sic] been carefully considered [sic]. However, absent a verified showing with a full explanation of the data, no patentable difference in structure is seen. Further, a mere difference in physical form absent a showing of unexpected properties does not establish a patentable distinction.

In response to this rejection, Glaxo submitted declarations to the patent office from John Harold Hunt, the head of Glaxo's Spectroscopy Unit, and David Trevor Collin, a research leader in the company's Chemical Development Department. Novopharm contends both of

these declarations contain intentional misrepresentations of material fact.

1. The Hunt Declaration.

Dr. John Harold Hunt's declaration set out the comparative results of certain analytical tests run on samples of Form 1 and Form 2 ranitidine hydrochloride. Dr. Hunt represented to the examiner that

> 3. Under supervision and/or at my direct request, the product of Example 1 of the present application i.e. Form 2 ranitidine hydrochloride and the product of Example **[**19]** 32 of US Patent *4128658* i.e Form 1 ranitidine hydrochloride have been examined using infra-red, n.m.r. and x-ray powder diffraction studies, and the results of these studies are reported below.
>
> * * *
>
> **[*878]** 5. Accompanying this declaration as Exhibit JHH 1 is a copy of the infrared spectrum . . . of Form 1 ranitidine hydrochloride. This is the material prepared according to Example 32 . . .
>
> * * *
>
> 7. The infrared spectra for Form 1 and Form 2 ranitidine hydrochloride were obtained in my Spectroscopy unit and the differences in main peak positions are such that it is clear that in the solid state the two products are not the same.
>
> 8. The present application also gives at page 4 'd' spacings obtained from the x-ray diffraction pattern for form 2 ranitidine hydrochloride . . . a comparison of this data with data obtained for Form 1 ranitidine hydrochloride by the same method is as follows:
>
> [Table showing comparisons is omitted]
>
> 9. . . . From a comparison of the respective 'd' spacings it is clear that there are very obvious and significant differences that confirm that in the solid state the two products do not have the same crystal structure.

Glaxo has stipulated that the infrared **[**20]** spectrum produced as Exhibit JHH1 with the Hunt Declaration was in fact not the result of a test run on a sample of Form 1 produced by Example 32; the sample tested in JHH1 was prepared using Process 3A. It is also Stipulated that no x-ray powder diffraction study was ever performed on a sample produced by the Example 32 process. Based on these facts, Novopharm argues that submission of the Hunt declaration constituted inequitable conduct.

On rebuttal, Glaxo produced evidence that Exhibit JHH1, although not prepared from an Example 32 sample, was identical to the spectrum prepared from Collin's experiment on page 122 of his notebook, and was the same within Scientific tolerances as all of the approximately one hundred and twenty five infrared spectra prepared from Form 1 samples. It was established by expert testimony that although x-ray powder diffraction can more accurately identify different crystalline forms, infrared spectroscopy is a good indicator of differences between polymorphs. For this reason, fewer x-ray powder diffraction studies were run by Glaxo, but the results of all the studies performed on Form 1 produced by means other than Example 32 were the same. Based **[**21]** upon this showing, Glaxo argued that there was no evidence of any material misrepresentation and no showing of intent to deceive the patent examiner.

There is no doubt that the Hunt declaration is misleading. The declaration represents that Exhibit JHH1 was prepared from an Example 32 sample. It was not appropriate to submit a spectrum prepared from a sample of any other process. The declaration also represents that "the product of Example 32" was subjected to x-ray powder diffraction, and this was in fact not true. These [HN5] misstatements only constitute inequitable conduct, however, if they were material and were submitted with intent to deceive the patent examiner.

Turning first to materiality, the court finds the misstatements were material. The patent examiner asked specifically for data showing the differences between the product of Example 32 and Form 2. The Hunt declaration purported to address that concern directly, but it did not. [HN6] "There is no room to argue that the submission of false affidavits is not material." *Rohm & Haas Co. v. Crystal Chemical Co., 722 F.2d 1556, 1571 (Fed. Cir. 1983)*, cert. denied *469 U.S. 851, 83 L. Ed. 2d 107, 105 S. Ct. 172 (1984)*. **[**22]**

In order to carry its burden on the element of intent, Novopharm urges the court to infer the necessary scienter from the circumstances surrounding the submission of the Hunt Declaration. Although circumstantial evidence and the context in which an affidavit is submitted may prove state of mind, *Paragon Podiatry Laboratory, Inc. v. KLM Laboratories, Inc., 984 F.2d 1182 (Fed. Cir.*

1993), the facts of this case do not warrant an inference of fraudulent intent.

While the court did not have the benefit of testimony from Dr. Hunt, n5 it is clear from the evidence that as head of the Spectroscopy Unit, he knew the infrared spectroscopy **[*879]** results of over one hundred Form 1 analyses had been the same. All of those analyses had shown different patterns than Form 2. Dr. Hunt also knew that the product of the very experiment on which Example 32 was based had been tested, and had produced results consistent with all other Form 1 infrared spectra. n6

n5 Dr. Hunt passed away in 1985.

n6 Even if the court accepted Novopharm's argument that the experiment on Collin's page 122 is not consistent with Example 32, there is no evidence that Dr. Hunt or anyone else at Glaxo suspected that there was any significant difference between the patent example and the work on which it was based.

[23]**

Considering Dr. Hunt's declaration in light of this knowledge, the court finds that the evidence does not support the inference that Dr. Hunt and the plaintiff intended to deceive the patent examiner by submitting Exhibit JHH1. Since the Example 32 data the examiner requested was identical to the 3A spectrum produced as Exhibit JHH1, neither Glaxo nor Dr. Hunt could have had anything to gain from the submission of the improperly identified exhibit.

With respect to the x-ray powder diffraction data, the court finds Novopharm has failed to show intent to deceive by clear and convincing evidence. The differences between Forms 1 and 2 of ranitidine hydrochloride are evident from infrared spectroscopy alone, and the powder diffractions, run on the two forms, confirmed the distinctions between the two polymorphs. Dr. Hunt had seen no differences in the infrared data between the product of Example 32 and other Form 1, and had no reason to believe that the x-ray data would differ, either. The court does not infer fraudulent intent from his submission of x-ray data from samples not prepared using Example 32.

Based on these findings, the court holds that Novopharm has failed to carry its burden **[**24]** of proving that Glaxo's submission of the Hunt Declaration constituted inequitable conduct in the prosecution of the *'431* patent.

2. The Collin Declaration.

In addition to the Hunt Declaration, Glaxo submitted to the patent office in 1983 the affidavit of David Trevor Collin, a Research Leader in Glaxo's Chemical Development Department. In this declaration, Collin represented to the examiner that Form 2 had certain qualities which made it less difficult and expensive to manufacture than the prior art. The first of these representations was that the Example 32 process requires the use of hydrogen chloride gas, which is corrosive, awkward to handle, and difficult to contain. By contrast, Collin's declaration says

> [Form 2] can most satisfactorily be prepared and isolated in a crystalline form in the presence of concentrated hydrochloric acid. This is surprising since ranitidine hydrochloride is sensitive to moisture and more significantly is highly soluble in water. The fact that Form 2 ranitidine hydrochloride can be prepared using concentrated hydrochloric acid is a very important and most significant factor since it avoids the need to use hydro-gen chloride gas and the attendant **[**25]** problems thereof.

Secondly, Collin represented to the examiner that

> My opinion, based on experience with the processes for preparing both Form 1 and Form 2 ranitidine hydrochloride, is that the product (Form 2) obtained from concentrated hydrochloric acid and isopropanol has better drying and filtration characteristics than the product (Form 1) obtained from the process using hydrogen chloride in industrial methylated spirit and ethyl acetate.

It is undisputed that between 1979 and 1980 Glaxo regularly prepared Form 1 using Process 3B, which requires the use of hydrochloric acid and isopropanol. From this fact, Novopharm argues the Collin Declaration is fraudulent because it suggests Form 1 cannot be made using hydrochloric acid, and that the ability to use hydrochloric acid is a distinguishing feature between the two polymorphs. Moreover, Novopharm contends Collin never compared the filtration and drying characteristic of Form 2 ranitidine hydrochloride with the product of example 32.

On rebuttal, Glaxo called Collin as a witness. He testified that at the time of **[*880]** the *'658* patent appli-

cation in 1977, and for some time after, Glaxo chemists were convinced that aqueous hydrochloric **[**26]** acid could not be used in the manufacture of ranitidine hydrochloride because the crystals were highly soluble in water. He further testified that his intent in preparing his declaration was to compare the art revealed in the *'658* patent with Form 2. Since the ability to use hydrochloric acid was not known in 1977, it was indeed surprising when compared to the prior art. Collin also testified that because Form 2 hydrochloride crystals are needlelike and Form 1 crystals are flatter and less three dimensional, Form 2 can be filtered and dried much more easily than Form 1, especially the Form 1 prepared using Process 3A.

The court found Collin's testimony credible on these points. Example 1 of the *'431* patent discloses the ability to use hydrochloric acid to make Form 2 ranitidine hydrochloride; the prior art of Example 32 discloses the ability to make ranitidine hydrochloride using hydrogen chloride in IMS. This difference between the *'431* patent and the prior art is significant. The evidence justifies Collin's conclusion that the ability to use aqueous hydrochloric acid was a surprising development over the prior art. There is no dispute that Form 2 has improved drying and filtration **[**27]** characteristics over Form 1 prepared using industrial methylated spirits and hydrogen chloride. Based upon these findings, the court concludes Collin made no misrepresentations of fact in his declaration. The submission of his declaration to the patent office cannot be the basis for a finding of inequitable conduct.

C. Failure to Disclose the Best Mode.

Novopharm's third reason for arguing the '438 patent be invalidated is its contention Glaxo failed to disclose the best mode of manufacturing Form 2 ranitidine hydrochloride for pharmaceutical use. [HN7] The patent statutes require, in addition to disclosing the invention itself, the applicant disclose in the patent specifications the best mode for making and using the claimed invention. *35 U.S.C. § 112.* The purpose of this requirement is to assure that in exchange for the monopoly protection extended by the grant of the patent, the applicant has given the public full access to the invention once the monopoly's protection is gone. See *Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1210 (Fed. Cir. 1991).*

The only evidence Novopharm presented on its best mode **[**28]** defense was the testimony of Graham George Brereton, who was the Glaxo employee responsible for directing the prosecution of the *'431* patent. n7 Brereton testified that prior to initiating the patent application, he met with research scientists within Glaxo to discuss what would be included in the patent specifications.

n7 Mr. Brereton was called by Novopharm as a hostile witness.

At the time of this meeting, Glaxo scientists recognized that ranitidine hydrochloride had poor flow properties and was therefore difficult to measure and dispense accurately in its pure form. In order to address this problem, Glaxo scientists had developed an "azeotroping" process by which ranitidine hydrochloride was granulated. Because granulation made ranitidine hydrochloride easier to measure and dispense accurately, azeotroping made it much simpler to formulate the salt into tablets, capsules and other pharmaceutical compositions. The azeotroping technique was a novel one, however, and Glaxo wished to retain it as a trade secret within **[**29]** the company. n8

n8 Glaxo filed a British patent application covering the azeotroping process, but eventually abandoned that application without ever making the process public.

Having been told of this novel azeotroping process that Glaxo wished to keep private, Brereton wrote to Glaxo's British patent agent, James Marchant, and informed him that he believed the best mode requirement in the United States would require Glaxo to disclose the azeotroping procedure if it included pharmaceutical composition claims in its U.S. patent application. In order to avoid the requirement that azeotroping be disclosed, he asked that no pharmaceutical composition claims be filed in the British patent application, so the two patents would be consistent. **[*881]** Because of this request, Marchant did not, at first, pursue composition claims in the British or American patent applications

In October of 1982, Brereton left his position as patent officer to take another job within Glaxo. On July 3, 1984, Glaxo amended its U.S. patent application **[**30]** covering Form 2 to include pharmaceutical composition claims, including tablets and capsules. The amendments did not reflect, however, that these compositions could best be made by utilizing the azeotroping technique.

It was Glaxo's contention at the close of Novopharm's evidence, the above showing was insufficient as a matter of law to establish a defense of invalidity in this case for two reasons. First, the only claims of the patent in suit infringed by Novopharm's ANDA were Claims 1 and 2, covering ranitidine hydrochloride, generally. The

pharmaceutical composition claims were not in issue, and therefore, even if there was a best mode violation concerning pharmaceutical compositions, Glaxo contends, it is not relevant in this case. Secondly, Glaxo argued even if others within Glaxo believed azeotroping was the best mode for using Form 2 ranitidine hydrochloride, Novopharm presented no evidence Dr. Derek Crookes, who is listed as the inventor of Form 2, knew of this best mode or attempted to conceal it.

The court finds the first of these arguments unavailing. [HN8] The best mode requirement imposes a duty to disclose not only the best mode of making the invention, but the best method **[**31]** of using it. *Chemcast Corp. v. Arco Industries Corp., 913 F.2d 923, 927 (Fed. Cir. 1990); Refac International Ltd. v. IBM, 689 F. Supp. 422, 431 (D.N.J. 1988).* Here, ranitidine hydrochloride is used not as a raw material, but as a drug administered to patients by means of some pharmaceutical composition. The court holds the failure to disclose the best mode of producing ranitidine hydrochloride for pharmaceutical use would affect the validity of claims covering the raw material.

With respect to the second of Glaxo's arguments, however, the court believes on the facts of this case, precedent dictates a finding of no best mode violation. In *Texas Instruments v. International Trade Commission, 871 F.2d 1054 (Fed. Cir. 1989)* the Federal Circuit upheld a finding that Texas Instruments had not violated the best mode requirement by failing to disclose a preferred method for boosting voltage on certain computer components on which it owned a patent. In that case the manufacturing group had developed a best mode which the company used commercially, but the person named as the inventor did not know **[**32]** of or conceal this best mode. The court found that the absence of a showing of actual knowledge by the inventor was dispositive of the defendant's best mode argument. *Id., at 1061.*

In the instant case, Brereton testified Dr. Derek Crookes, who was listed as the inventor in the patent, was not consulted in making this decision, and it was his belief Crookes did not know the azeotroping procedure was the best mode for manufacturing ranitidine hydrochloride for pharmaceutical use. The court found Brereton to be a credible witness, and therefore, cannot find as a fact Crookes knew azeotroping was the preferred mode or attempted to conceal such preferred mode in the *'431* patent application. It is undisputed, however, Brereton and other officers within Glaxo believed azeotroping was the best mode of preparing ranitidine hydrochloride for pharmaceutical use, and Glaxo actually utilized this method in the commercial production of ranitidine hydrochloride. These officials within Glaxo made a deliberate choice not to reveal what they believed to be the best mode of making the patented invention, but instead to protect the knowledge as a trade secret. n9

n9 Because none of Novopharm's evidence on its best mode defense was disputed, the court ruled at the close of Novopharm's case-in-chief that the best mode issue would be decided as a matter of law at the conclusion of the trial.

[33]**

Novopharm argued at trial that the knowledge of Glaxo officials directly connected to the application for the patent should be imputed to Crookes for purposes of finding a best mode violation. This argument has some intuitive appeal, since it is Glaxo, and not Crookes individually, that both directed **[*882]** the patent prosecution and has enjoyed the monopoly the issued patent provides. If the court were to impute to Crookes the knowledge of Brereton and those with whom he met prior to the patent application process, then clearly the court would be required to find a best mode violation.

[HN9] The statute refers only to the knowledge of the inventor, however, *35 U.S.C. § 112,* and the holding of the Federal Circuit in the Texas Instruments case does not permit using imputed knowledge to meet the requirement. The court concludes as a matter of law Novopharm failed to show the *'431* patent should be invalidated based on a best mode violation.

III. CONCLUSION

Based on the evidence, Novopharm has failed to carry its burden on the defense of invalidity. The court holds that United States Patent No. *4,521,431* is not invalid, and that Novopharm infringed the **[**34]** patent by filing its ANDA on August 9, 1991. On this finding, it is ORDERED pursuant to *35 U.S.C. § 271* (e)(4) Novopharm not be granted approval to sell Form 2 ranitidine hydrochloride prior to the expiration of the *'431* patent. Defendant Novopharm is further ORDERED to refrain from the commercial manufacture or sale within the United States of Form 2 ranitidine hydrochloride prior to the expiration of the *'431* patent. ORDERED this 17th of September, 1993.

TERRENCE W. BOYLE, UNITED STATES DISTRICT JUDGE